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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
KUMAR, SHAILENDRA	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
08/03/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,518	SPERL, STEFAN	
	Examiner	Art Unit	
	SHAILENDRA -. KUMAR	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/9/07 has been entered.

Claims 1-18 are pending in this application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The treatment/prevention of cancers generally cannot possibly be considered enabled.

By way of background, four cases are of particular relevance to the question of enablement of a method of treating cancers broadly or even generally:

In *In re Buting*, 57 CCPA 777, 418 F.2d 540, 163 USPQ 689, the claim was drawn to "The method of treating a malignant condition selected from the group consisting of leukemias, sarcomas,

adenocarcinomas, lymphosarcomas, melanomas, myelomas, and ascitic tumors" using a small genus of compounds. The Court decided that human testing "limited to one compound and two types of cancer" was not "commensurate with the broad scope of utility asserted and claimed".

In *Ex parte Jovanovics*, 211 USPQ 907 the claims were drawn to "the treatment of certain specified cancers in humans" by the use of a genus of exactly two compounds, the N-formyl or N-desmethyl derivative of leurosine. Applicants submitted "affidavits, publications and data" for one of the compounds, and a dependent claim drawn to the use of that species was allowed. For the other, no data was presented, applicants said only that the other derivative would be expected to be less effective; claims to the genus were refused.

In *Ex parte Busse*, et al., 1 USPQ2d 1908, claims were drawn to "A therapeutic method for reducing metastasis and neoplastic growth in a mammal" using a single species. The decision notes that such utility "is no longer considered to be "incredible", but that "the utility in question is sufficiently unusual to justify the examiner's requirement for substantiating evidence. Note also that there is also a dependent claim 5 which specified "wherein metastasis and neoplastic growth is adenocarcinoma, squamous cell carcinoma, melanoma, cell small lung or glioma." The decision notes that "even within the specific group recited in claim 5 some of the individual terms used actually encompass a relatively broad class of specific types of cancer, which specific types are known to respond quite differently to various modes of therapy."

In *Ex parte Stevens*, 16 USPQ2d 1379 a claim to " A method for therapeutic or prophylactic treatment of cancer in mammalian hosts" was refused because there was "no actual evidence of the effectiveness of the claimed composition and process in achieving that utility."

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation

needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds.

(b) Scope of the diseases covered. The coverage is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body. Here are some assorted categories:

A. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. Gliomas, the most common subtype of primary brain tumors, most of which are aggressive, highly invasive, and neurologically destructive tumors are considered to be among the deadliest of human cancers. These are any cancers which show evidence (histological, immunohistochemical, ultrastructural) of glial differentiation These fall mostly into five categories. There are the astrocytic tumors (Astrocytomas): Pilocytic astrocytoma (including juvenile pilocytic astrocytoma, JPA, and pediatric Optic Nerve Glioma) Diffuse astrocytomas (including Fibrillary astrocytomas, Protoplasmic astrocytomas and Gemistocytic astrocytomas), Anaplastic astrocytomas (including adult Optic Nerve Glioma), Glioblastoma multiforme (GBM), gliosarcoma and giant cell glioblastoma, and Pleomorphic xanthoastrocytoma. GBM exists in two forms, primary and secondary, which have very different clinical histories and different genetics, but GBM is considered to be one clinical entity. Second, there are the oligodendroglial tumors (Oligodendrogliomas): Low grade Oligodendroglioma and Anaplastic Oligodendroglioma. Third, there is oligoastrocytomas ("mixed glioma"), a type of tumor with both astrocytoma & oligodendroglioma features. The fourth type is the Ependymomas, which are intracranial gliomas, including Papillary Ependymoma, Myxopapillary ependymoma, tanycytic ependymoma, Anaplastic ependymoma and subependymal giant-cell astrocytomas. A fifth type is

the Gangliogliomas (glioneuronal tumors or glioneurocytic tumors), which have both glial and neuronal components, and are extremely varied, based in part on what types of glial and what types of neuronal components are present. These include Papillary Glioneuronal Tumor (PGNT), a range of Supratentorial gangliogliomas, assorted intramedullary spinal cord gangliogliomas, Pineal ganglioglioma, Hypothalamic ganglioglioma, cerebellar ganglioglioma, Ganglioglioma of the right optic tract, rosetted glioneuronal tumor ("glioneurocytic tumor with neuropil rosettes"), composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma, desmoplastic ganglioglioma (both infantile (DIG) and non- infantile), Angioganglioglioma, and others. There are also some Glial tumors which do not comfortably fit into these five categories, notably Astroblastoma, Gliomatosis cerebri, and chordoid glioma, which is found solely in the Hypothalamus and Anterior Third Ventricle. Other neuroepithelial tumors include astrocytic tumors (e.g. astrocytomas) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus(Choroid plexus papilloma, Choroid plexus carcinoma), assorted neuronal and Neuroblastic tumors (e.g. gangliocytoma, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma, Olfactory neuroblastoma, Olfactory neuroepithelioma, and Neuroblastomas of the adrenal gland), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma, and Pineal parenchymal tumor of intermediate differentiation), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma, Atypical teratoid/rhabdoid tumor, Desmoplastic medulloblastoma, Large cell medulloblastoma, Medullomyoblastoma, and Melanotic medulloblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (Meningothelial, Fibrous (fibroblastic), Transitional (mixed), Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Metaplastic, Clear cell, Chordoid, Atypical, Papillary, Rhabdoid, Anaplastic meningioma) and the non- Meningioma tumors of the meningothelial cells (Malignant fibrous histiocytoma, Leiomyoma, Leiomyosarcoma, Rhabdomyoma,

Rhabdomyosarcoma, Chondroma, Chondrosarcoma, Osteoma, Osteosarcoma, Osteochondroma, Haemangioma, Epithelioid haemangioendothelioma, Haemangiopericytoma, Angiosarcoma, Kaposi sarcoma). There are also Mesenchymal, non-meningothelial tumors (Lipomas, Angiolipoma, Hibernoma Liposarcoma, (intracranial)Solitary fibrous tumor, and Fibrosarcoma) as well as Primary melanocytic lesions (Diffuse melanocytosis, Melanocytoma, Malignant melanoma, and Meningeal melanomatosis). A third Division are the tumors of Cranial and Spinal Nerves. This includes Cellular schwannomas, Plexiform schwannomas and the Melanotic schwannomas (e.g. psammomatous melanotic schwannoma , Neuro-axial melanotic schwannoma, **Dorsal dumb-bell melanotic schwannoma). There is also** neurofibroma, Perineurioma (Intraneural and Soft tissue) and malignant peripheral nerve sheath tumor (MPNST), including Epithelioid, MPNST with divergent mesenchymal differentiation, and MPNST with epithelial differentiation. A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (Mature teratoma, Immature teratoma, and Teratoma with malignant transformation). A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma, granular cell myoblastoma and craniopharyngiomas (Adamantinomatous and pillary). Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. There are also Primitive Neuroectodermal Tumors (PNETs) including Medulloblastomas, medulloepitheliomas, ependymoblastomas and polar spongioblastomas. There are Vascular brain Tumors e.g. the hemangioblastomas, there is CNS Lymphoma (which can be primary or secondary) and Meningeal Carcinomatosis. There are Lymphoma AND Haemopoietic neoplasms including Malignant lymphomas (which can be primary or secondary), Plasmacytoma, and Granulocytic sarcoma. And there are many, many others. Although claim 6 is drawn to pancreatic cancer and claim 7 is drawn to pemphigus vulgaris, nevertheless, the prevention is impossible.

B. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic Lymphoid leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, adult T cell leukemia/lymphoma (ATLL), and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias (undifferentiated AML, acute myeloblastic, acute myelomonocytic leukemia, acute monocytic leukemias, acute monoblastic, acute megakaryoblastic (AmegL), acute promyelocytic leukemia (APL), and erythroleukemia). There is also lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, and acute basophilic leukemia. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia(CEL), and many others.

C. Carcinomas of the Liver include Hepatocellular carcinoma, Combined hepatocellular cholangiocarcinoma, Cholangiocarcinoma (intrahepatic), Bile duct cystadenocarcinoma and Undifferentiated carcinoma of the liver. There are also two types of liver hemangioma: cavernous and hemangioendothelioma.

D. The main types of lung and pleural cancer are small cell (i.e. oat cell, including combined oat cell), adenocarcinoma (Bronchioloalveolar carcinomas (Nonmucinous, Mucinous, and Mixed mucinous and nonmucinous or indeterminate cell type), Acinar, Papillary carcinoma, Solid adenocarcinoma with mucin, Adenocarcinoma with mixed subtypes, Well-differentiated fetal adenocarcinoma, Mucinous (colloid) adenocarcinoma, Mucinous cystadenocarcinoma, Signet ring adenocarcinoma, and Clear cell adenocarcinoma), squamous cell (Papillary, Clear cell, Small cell and Basaloid), mesothelioma (including epithelioid, sarcomatoid, desmoplastic and biphasic) and Large Cell Carcinoma (which include Large-cell neuroendocrine carcinoma, Combined large-cell neuroendocrine carcinoma, Basaloid carcinoma, Clear cell carcinoma Lymphoepithelioma-like carcinoma, and Large-cell carcinoma with rhabdoid phenotype). In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including Carcinomas with spindle and/or giant cells, Spindle cell carcinoma, Carcinosarcoma and Pulmonary blastoma. The non-small cell lung carcinomas also include Adenosquamous carcinoma, the Carcinoid tumor (both typical Carcinoid and atypical Carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma. There are some soft tissue tumors including localized fibrous tumor (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma; pleuropulmonary blastoma; chondroma; calcifying fibrous pseudotumor of the visceral pleura); congenital peribronchial myofibroblastic tumors, diffuse pulmonary lymphangiomyomatosis and desmoplastic round cell tumor. There are assorted bronchial adenomas (eg, adenoid cystic carcinomas, mucoepidermoid carcinomas, mucous gland adenomas, and oncocytomatous bronchial mucous gland adenoma) as well as other adenomas, including papillary adenoma. There are some papillomas, including squamous cell papilloma and glandular papilloma. There is also malignant melanoma of

the lung, Hamartoma, cylindroma (cylindroadenoma), some germ cell tumors, thymoma and sclerosing haemangioma and many others as well.

E. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

F. Carcinomas of the skin are the Basal cell carcinomas (BCC), including Superficial BCC, Nodular BCC (solid, adenoid cystic), Infiltrating BCC, Sclerosing BCC (desmoplastic, morpheic) , Fibroepithelial BCC, BCC with adnexal differentiation, Follicular BCC, Eccrine BCC, Basosquamous carcinoma, Keratotic BCC, Pigmented BCC, BCC in basal cell nevus syndrome, Micronodular BCC. Another important family is the Squamous cell carcinomas (SCC) which include Spindle cell (sarcomatoid) SCC, Acantholytic SCC, Verrucous SCC, SCC with horn formation, and Lymphoepithelial SCC, along with less well classified SCCs such as Papillary SCC, Clear cell SCC, Small cell SCC, Posttraumatic (e.g., Marjolin ulcer) and Metaplastic (carcinosarcomatous) SCC. Another family is the Eccrine carcinomas including Sclerosing sweat duct carcinoma (syringomatous carcinoma, microcystic adnexal carcinoma), Malignant mixed tumor of the skin (malignant chondroid syringoma), Porocarcinoma, Malignant nodular hidradenoma, Malignant eccrine spiradenoma, Mucinous eccrine carcinoma, Adenoid cystic eccrine carcinoma, and Aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include Epidermal carcinomas, Paget disease, Mammary Paget disease, Extramammary Paget disease Adnexal carcinomas, Apocrine carcinoma, Sebaceous carcinoma, Tricholemmocarcinoma and Malignant pilomatricoma (matrical carcinoma).

G. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type,

lymphomas, melanomas (which can be primary or metastatic), sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors.

H. Renal carcinomas include papillary renal cell carcinoma, conventional-type (clear cell) renal carcinoma, chromophobe renal carcinoma, collecting duct carcinoma, and some unclassified cancinomas. Other kidney cancers include Transitional Cell Carcinoma, Wilms Tumors, and Renal Sarcomas.

I. Carcinomas of the prostate are usually adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma of the prostate, basal cell carcinoma, neuro-endocrine carcinoma, signet-ring cell carcinomas and others.

J. Penile carcinoma is usually a squamous cell carcinoma, but there is also Penile clear cell carcinoma and Sarcomatoid carcinoma.

K. The carcinomas of the extrahepatic bile ducts are of numerous types, including carcinoma in situ, Adenocarcinoma, Papillary adenocarcinoma, Adenocarcinoma (intestinal-type), Mucinous adenocarcinoma, Clear cell adenocarcinoma, Signet ring cell carcinoma, Adenosquamous carcinoma, Squamous cell carcinoma, Small cell carcinoma (oat cell carcinoma) and undifferentiated carcinoma of the extrahepatic bile ducts.

L. Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers. These come in a wide variety of types. Presently, these are divided into the following categories: Intraductal (in situ); Invasive with predominant intraductal component; Invasive, NOS; Comedo; Inflammatory (IBC); Medullary with lymphocytic infiltrate; Mucinous Carcinoma (colloid carcinoma); Papillary carcinoma; Scirrhous; Tubular; and Other. Another category is the Lobular breast cancers, which can be in situ, Invasive with predominant in situ component, and Invasive. There is Paget's disease of the Nipple, which can be also with intraductal carcinoma or with invasive

ductal carcinoma. There is Adenomyoepithelioma , a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of the breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides, and liposarcoma of the breast. There are carcinoid tumors which can be primary carcinoid tumors of the breast, or can arise from from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary epithelial oncocytoma), and mucoepidermoid carcinoma (MEC). Other rare carcinomas include Spindle cell carcinoma of the breast (SpCC), Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including for example Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast, and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas, and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus, and colon).

M. Ovarian cancers are a heterogeneous group of tumors. The most important are the epithelial tumors. These are themselves fairly diverse, the categories being Serous cystomas (Serous benign cystadenomas, Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth and Serous cystadenocarcinomas); Mucinous cystomas (divided the same three ways); Clear cell tumors (mesonephroid tumors, again

divided the same way), Endometrioid tumors (similar to adenocarcinomas in the endometrium: Endometrioid benign cysts, Endometrioid tumors with proliferating activity of the epithelial cells and Endometrioid adenocarcinomas), mixed mesodermal (now considered to be carcinomas with areas of sarcomatous differentiation), clear cell, transitional cell, and mixed epithelial. Second, there are the Granulosa-Stromal Cell Tumors. These include the Granulosa cell tumor (which exists in juvenile and adult forms) and the tumors in the thecoma-fibroma group. This includes thecoma-fibroma group typical thecoma and luteinized thecoma or "stromal Leydig cell tumor". This also includes fibroma, cellular fibroma, fibrosarcoma, stromal tumor with minor sex cord elements, sclerosing stromal tumor, signet ring cell stromal tumor and others. Third, there are the Sertoli-Leydig Cell Tumors and Androblastomas. These include the Sertoli cell tumor (tubular androblastoma), Sertoli-Leydig cell tumor , a poorly differentiated sarcomatoid, tumor and a Retiform tumor. Fourth, there are some miscellaneous Sex Cord Stromal Tumors, including Gynandroblastoma of the ovary (composed of sex cord and stromal cells of both ovarian and testicular types), Sex Cord Tumor with Annular Tubules, Stromal luteoma, and Leydig cell tumor)which comes in hilus and non-hilar types). Fifth, there are an assortment of Germ Cell Tumors. These include Dysgerminoma; Yolk Sac Tumors (Endodermal Sinus Tumor, and Polyvesicular vitelline tumor, Hepatoid and others); Embryonal Carcinoma; Polyembryoma; Choriocarcinoma and a wide variety of Teratomas. These tetromas include immature, cystic (dermoid cyst), retiform (homunculus), and Monodermal, including struma ovarii, carcinoid (insular and trabecular), struma carcinoid, mucinous carcinoid, neuroectodermal tumors, sebaceous tumors and others. Finally, there are an assortment of other tumors which do not fit into the above categories. There is Gonadoblastoma and Tumors of Rete Ovarii (which c an be Adenomatoid tumor or a Mesothelioma). There are some tumors of Uncertain Origin, including Small cell carcinoma, tumors of probable Wolffian origin, a Hepatoid carcinoma and Oncocytoma. There are some Soft Tissue Tumors not Specific to Ovary, and there are assorted malignant Lymphomas and Leukemias which land up in the ovaries.

N. Cervical cancers. There are many different categories and sub-categories of cervical cancers. The majority of cervical cancers are Squamous Cell Carcinomas. These come in numerous types: large cell nonkeratinizing type; large cell keratinizing type; Basaloid; Verrucous; Warty; Papillary; Lymphoepithelioma-like; and Squamotransitional, Early invasive (microinvasive) squamous cell carcinoma; Squamous intraepithelial neoplasia (including Cervical intraepithelial neoplasia and Squamous cell carcinoma in situ). There are also a variety of Adenocarcinomas, the most important of which are the Mucinous adenocarcinoma, which include the Endocervical, Intestinal, signet-ring cell, minimal deviation, and Villoglandular. There is also Endometrioid adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, Mesonephric adenocarcinoma, Early invasive adenocarcinoma, and Adenocarcinoma in situ. In addition, there are neuroendocrine carcinomas, divided into Small Cell, large cell, classical carcinoid and atypical carcinoid. Other epithelial tumors include Adenosquamous carcinoma, mixed Adenosquamous Carcinomas, which can be either well-differentiated or poorly differentiated, the latter including glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal carcinoma and Undifferentiated carcinoma. There are also some mixed carcinoma with signet-ring cells, and other types of other poorly differentiated mixed carcinomas. This group includes tumors sometimes called apudomas or argyrophil cell carcinomas. There are also an assortment of Mesenchymal tumors of the cervix, including Leiomyosarcoma; Endometrioid stromal sarcoma, low grade; Undifferentiated endocervical sarcoma; Sarcoma botryoides; Alveolar soft part sarcoma, Angiosarcoma of the cervix, Malignant peripheral nerve sheath tumor of the cervix; Cervical leiomyoma; and Rhabdomyoma of the cervix. There are also some mixed epithelial and mesenchymal tumors, including Carcinosarcoma (malignant

müllerian mixed tumor), Adenosarcoma, Wilms tumor, typical and atypical Polypoid Adenomyoma, and Papillary adenofibroma of the cervix. There are also Melanocytic tumors, including primary malignant melanoma of the cervix and Blue naevus of the cervix. There are also germ cell type tumors, including Yolk sac tumor, Dermoid cyst, and Mature cystic teratoma of the cervix. There is also primary choriocarcinoma of the cervix, which does not fit well into any category. There are also cancers secondary to the cervix, which have spread from elsewhere.

O. Bladder cancers. Most cases of bladder cancers are transitional cell (urothelial) carcinoma, which includes non-invasive papillary urothelial carcinoma, Flat urothelial carcinoma in situ (CIS), Superficially invasive urothelial carcinoma, and muscle invasive tumors. Adenocarcinomas of the bladder include Primary Adenocarcinoma (urachal and non-urachal), Prostatic adenocarcinoma, Gastro-intestinal adenocarcinomas and Clear cell carcinoma. Squamous cell carcinomas include Verrucous carcinomas, and a secondary squamous cell carcinoma of the bladder, from the cervix. Small cell carcinomas include Primary small cell carcinoma of the bladder and the secondary small cell carcinoma ('reserve cell carcinoma') of the lung. Lymphomas include the primary lymphomas (Low grade B-cell lymphoma of MALT type, High grade B-cell lymphoma, and T-cell lymphoma), as well as secondary lymphomas, including mantle cell lymphomas. Melanomas include Primary Malignant melanoma of the bladder, and secondary ones. The sarcomas of the Bladder are Leiomyosarcoma, Osteosarcoma and Rhabdomyosarcoma. There is also a primary primitive neuroectodermal tumour (PNET) of the bladder, Paraganglioma (which can metastasize), Nephrogenic adenoma, Metastatic renal cell carcinoma of the bladder, and both primary and secondary (from the uterus) Choriocarcinoma of the bladder.

P. Cancers of the Vulva are mostly Squamous carcinoma, but these also include Melanoma, Bartholin's Adenocarcinoma, Basal Cell carcinoma and some Sarcomas.

Q. Vaginal cancers are primarily Squamous Carcinoma, but some are

Adenocarcinoma, Melanoma of the vagina; Sarcoma of the vagina, Bowen's disease and Germ Cell Tumors.

R. The most important of the cancers of the uterus are the Endometrial Carcinomas. The great majority of these are Endometrioid; others include Uterine Papillary Serous Tumor (UPST), Clear Cell Carcinoma, Mucinous and Squamous. Uterine Sarcomas include Smooth Muscle Tumors include leiomyoblastoma, clear cell leiomyoma, epithelioid leiomyoma, plexiform tumorlet, Intravenous leiomyomatosis, Benign metastasizing leiomyoma, Leiomyomatosis peritonealis disseminate and Leiomyosarcoma (LMS). Endometrial Tumors include Endometrial stromal nodule, Endolymphatic stromal myosis, (ESM) and Endometrial stromal sarcoma (ESS). There are the mixed tumors Müllerian adenosarcoma and Malignant mixed mesodermal tumors (MMMT). Other sarcomas are Rhabdosarcoma, Osteosarcoma, Chondrosarcoma nad Hemangiopericytoma. There are also uterine cancers which do not come from uterine cells themselves, but start in the tissue that begins to develop immediately after conception: Persistent gestational trophoblastic disease, choriocarcinoma and placental site trophoblastic tumors (PSTT).

(2) The nature of the invention and predictability in the art: With specific reference to cancer, *Ex parte Kranz*, 19 USPQ2d 1216, 1219 notes the "general unpredictability of the field [of] ...anti-cancer treatment." *In re Application of Hozumi et al.*, 226 USPQ 353 notes the "fact that the art of cancer chemotherapy is highly unpredictable". More generally, the invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided Further, it is completely generic. That is, it is the same dosage for all disorders listed in the specification, which is a very substantial range of disorders.

In terms of specific cancers,

(4) State of the Prior Art: The claimed compounds are . So far as the examiner is aware have not been successfully used as anticancer agents.

(5) Working Examples:

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally." (<<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7>> ENABLEMENT DECISION TREE, Example F, situation 1) There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is because it is now understood that there is no "master switch" for cancers generally; cancers arise from a bewildering variety of differing mechanisms. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (an estimated at least 20% are of viral origin e.g. EBV, HHV-8, HTLV-1 and other retroviruses), exposure to chemicals such as tobacco tars, genetic disorders (e.g. Tuberous Sclerosis), ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Cancers that affect just a certain type of structure can be quite varied. Fibromas for example include Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic

fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are a few cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. With regard to gliomas, GBM is considered untreatable; no effective agents have emerged for the treatment of GBM, despite 20 years of enrolling patients in clinical trials. It is radiation and surgery which are used for low grade gliomas (e.g. Pilocytic astrocytoma and Diffuse astrocytomas), as no drug has been found effective. There is no drug treatment established as effective for optic nerve gliomas or gangliogliomas. Indeed, very few gliomas of any type are treated with pharmaceuticals; it is one of the categories of cancer that is the least responsive to drugs. Cartilage tumors do not respond to chemotherapy, nor do Cancerous teratomas. Of the thyroid cancers, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones. Neuroendocrine tumors of the cervix generally do not respond to chemotherapy. Renal cell carcinoma does not respond to chemotherapy. A number of sarcomas, including Alveolar soft part sarcoma (ASPS), retroperitoneal sarcoma, most liposarcomas, and the assorted chondrosarcomas, are generally considered not to respond to chemotherapy; no chemotherapeutic agent has been established as effective. **Aggressive NK cell leukemia is considered to be**

untreatable with pharmaceuticals. Many cerebral metastases, such as those from non-small-cell lung cancer and melanoma, are not chemosensitive and will not respond to chemotherapy. Hepatocellular Carcinoma is, in humans, possibly the most prevalent solid tumor. Despite strenuous efforts over a period of decades, no chemotherapeutic agent has ever been found effective against this cancer.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 4, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 103

4. Claims 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over combined teachings of combined teachings of WO 92/08709 and WO 00/17158.

Instant claims are directed to Guanidino phenylalanine compounds and their pharmaceutical compositions.

WO'709 teaches structurally similar compounds and composition as claimed herein. Note, page 6, wherein R1 can be guanidine as well as amidine, R2 can be OH or OR, R4 can be substituted or unsubstituted phenyl and R3 can be H or alkyl. The difference between the reference and herein claimed subject matter is that the reference compounds are used for blood coagulation as against urokinase inhibition method in herein.

W0'158 is cited to show that the structurally similar compounds as claimed herein can be used as urokinase inhibitors, see pages 2-7.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the compounds of W0'709 in the method of inhibition of urokinase, as taught by W0'158, because the latter reference is expressly teaching that structurally similar compounds as claimed can be used in the inhibition of urokinase. Note the equivalence of guanidine and amidino group taught by W0'709.

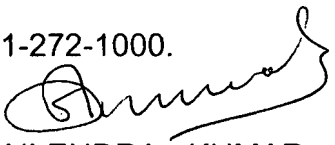
Applicants' arguments were fully considered and were not found convincing. Applicants argue that the compounds disclosed in WO '158 are quite different from the compounds recited in present claims. The WO '158 compounds are all amidino compounds *(Le.,* they all have the C(NH)(NH2) substituent on the phenyl ring), whereas the presently claimed compounds are all guanidino compounds having the NH-C(NH)NH2 substituent on the phenyl ring. Even with WO '158 in hand, one of ordinary skill would not be led to substitute a guanidino group for an amidino group. There is no suggestion from the references that one would expect guanidino compounds to be urokinase inhibitors from the mere fact that amidino compounds are urokinase inhibitors, and both amidino and guanidino compounds inhibit thrombosis. WO '158 suggests many variables in other portions of the molecule, but all of the compounds contain the amidino group, with no suggestion of variation at that point. It is respectfully submitted that it is only in hindsight with the benefit of the present applicant's specification can it be said to be obvious to modify the WO '158 compounds as posited. Moreover, even if there were motivation in the art to make that change, one would still not have the necessary expectation of success after the modification was made. The references relied on do not provide any structure/activity link between amidino and guanidine groups in the context of inhibiting urokinase activity.

The examiner respectfully disagrees. A mere fact that there is equivalence of amidino and guanidine group, one of ordinary skill in the art would expect the compounds to behave both as urokinase inhibitors as well as blood coagulators. Applicants' arguments regarding the unexpected results is not convincing inasmuch as side by side comparison has not been done. Applicants finally argue that WO'709 fails to teach R2 to be trisubstituted phenyl group. The examiner would like to point out to WO'158 which expressly suggest R2 to be trisubstituted phenyl group.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHAILENDRA -. KUMAR whose telephone number is (571)272-0640. The examiner can normally be reached on Mon-Thur 8:00-5:30, Alt Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SHAILENDRA - KUMAR
Primary Examiner
Art Unit 1621

S.Kumar
7/30/07